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May 16, 2005

Sheldon T. Bradshaw, Esq.
FDA Chief Counsel
c/o Mr. Vincent de Jesus
Food and Drug Administration (HFS-830)
5100 Paint Branch Parkway
College Park, MD 20740-3835 Via Federal Express #842881989070

Re: Application: Docket No. 2004Q-0083-Daily consumption of 40 ounces of typical green tea containing 710μg/mL natural (-)-epigallocatechin gallate (EGCG) may reduce the risk of certain forms of cancer....

Dear Mr. Bradshaw:

For your reference, I am enclosing a copy of the most recent review article entitled "Green Tea: Health Benefits as Cancer Preventive for Humans" by Hirota Fujiki (1) while you are completing the scientific review of my said application. Dr. Fujiki is one of the world-recognized authorities on this subject and the scientific evidence cited in this review article renders independent support of the green tea qualified health claim proposed in my application under Docket No. 2004Q-0083. Please note the following points made in his review.

1) The term "cancer chemoprevention" was coined by the scientists at the National Cancer Institute in the United States in 1976.

2) Green tea is now an acknowledged cancer preventive in Japan.

3) The effective cancer preventive amount of green tea is determined to be 10 Japanese-sized cups (about 120 ml/cup) per day, i.e. 1,200 ml as proposed in the claim under Docket No. 2004Q-0083.

4) Sencha which means *"loose tea leaves"* is the most popular kind of green tea in Japan and the typical Sencha contains 7.51% EGCG, as compared to the lower grade of Sencha commonly referred to as Hojicha and oolong (partially green) tea which contain 1.68% and 4.67% EGCG respectively.

[Note: The FDA has the responsibility to educate the American consumers on this point. The green tea leaves to be used for health protection should have at least extractable 7% EGCG. Most people used 1% w/v leaf to water ratio to make tea drinks that do not meet the health protection recommendation.]

5) Dr. Fujiki derived his primary human study data from Saitama, a traditionally green tea producing and consuming region based on the initial introduction of green tea as medicine by a Japanese priest, Eisai, in 1191 A.D. from China during the **Southern Song** dynasty (1127-1276 A.D.). The capital of China then was in Hangzhou. Hangzhou has been known to be the "Capital of Green Tea" in China.

[Note: Please refer to my application in which I have brought to the attention of the FDA that the NCI specification for "typical" green tea recommended for cancer research was based on data derived from the green tea drink traditionally consumed in Hangzhou, setting 710 micrograms/ml EGCG as the standard.]

2004Q-0083

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6) Cancer onset of patients who had consumed over 10 cups of green tea per day was 7.3 years later among females and 3.2 years later among males as compared to those drinking less than three cups per day.

7) In stage I and II breast cancer patients, the group consuming over 5 cups per day showed a significantly lower recurrence rate and a longer disease-free period.

I hope this enclosed article may serve as supplementary material in expediting the reviewing process in the Office of the Chief Counsel. If you have any question about my application, please call my office and I will provide an answer immediately. It is disappointing to observe too much half-true information has been exploited by many tea vendors to promote their products at the expense of the consumer health. I urge the Office of the FDA Chief Counsel to facilitate the decision on the green tea health claim to guide the consumers and the industry without further delay because the American consumers need the FDA guidance to select the right kind of tea used for its health benefits.

A copy of the FDA Dockets of the year 2004 downloaded from the Internet has been enclosed (2). According to the dates of acceptance for official filing, the next application in line for an FDA decision is the green tea qualified health claim petition under Docket No. 2004Q-0083. I request the Office of the Chief Counsel to observe the internal rules and regulations of the FDA, if they exist, to make decision on applications according to chronological order unless there is a scientific reason for an exception which I should be notified of immediately and be given a chance to respond to.

Thank you for your attention and cooperation.

Sincerely,

Sin Hang Lee

Sin Hang Lee, M.D.

References (copies enclosed)

(1) Fujiki H. Green tea: Health benefits as cancer preventive for humans. Chem Rec. 2005;5:119-132.
(2) FDA Dockets of the year 2004.

cc. Dr. Lester Crawford, Acting Commissioner of FDA; Senator Chris Dodd; Senator Joe Lieberman; Senator Mike Enzi; Congresswoman Rosa L. DeLauro; Congressman Christopher Shays; Congresswoman Nancy L. Johnson; Congressman John B. Larson; Congressman Rob Simmons; The Inspector General, HHS; The U.S. Surgeon General.

Green Tea: Health Benefits as Cancer Preventive for Humans

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Received 27 December 2004; Revised 11 March 2005; Accepted 2 March 2005

ABSTRACT: Green tea is an acknowledged cancer preventive in Japan. The aim of this review article is to develop the concept of cancer prevention with green tea beverage for humans, which has largely been our exclusive research territory. This paper briefly reviews several topics, beginning with the introduction of our initial work on penta-O-galloyl-β-D-glucose and (–)-epigallocatechin gallate (EGCG), the main constituent of green tea extract. The mechanisms of EGCG action, particularly the reduction of TNF-α are discussed, and we show how use of ^{3}H-EGCG revealed a wide range of target organs for cancer prevention. The results of an epidemiological study in Saitama Prefecture allowed us to determine the cancer preventive amount of green tea—10 Japanese-size cups per day, about 2.5 g green tea extract—which made it possible for us to introduce the two-stage strategy of cancer prevention with green tea. The first stage is the delay of cancer onset for the general population. The second stage is the prevention of recurrence of cancer for patients following cancer treatment. Combination cancer prevention with green tea and cancer preventive drugs is proving especially beneficial for Japanese, who drink green tea every day. And finally, the stimulating comments of Prof. Jim Watson have encouraged green tea scientists. © 2005 The Japan Chemical Journal Forum and Wiley Periodicals, Inc. Chem Rec 5: 119–132; 2005: Published online in Wiley InterScience (www.interscience.wiley.com) DOI 10.1002/tcr.20039

Key words: EGCG; sealing effects; 10 Japanese-size cups; combination cancer prevention; *GADD153* gene

Introduction

Cancer chemoprevention is a relatively new medical strategy for cancer prevention, a strategy that was established through recent understanding of molecular multistage carcinogenesis in humans. The term "cancer chemoprevention" was coined by Michael Sporn et al. at the National Cancer Institute in the United States in 1976, and defined as the prevention of the occurrence of cancer by administration of one or several compounds.[1] In 1983, when research in cancer chemoprevention began in Japan, we sought to identify original Japanese cancer preventive agents,[2] and Prof. Takuo Okuda at the Faculty of Pharmaceutical Sciences, Okayama University, gave us tannins or polyphenols derived from medicinal plants and drugs. However, a working group of the International Agency for

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Research on Cancer (IARC) in France had reported in 1975 that tannin was a carcinogen,[3] so we had to determine whether Okuda's polyphenols would act as carcinogens or non-carcinogens. Therefore, Okuda's 30 polyphenols were first tested to find out whether they shared the same phorbol ester receptor in a membrane fraction of mouse skin as did 12-*O*-tetradecanoylphorbol-13-acetate (TPA), a classic tumor promoter (Figure 1).[4]

Two polyphenols, penta-*O*-galloyl-β-D-glucose (5GG)—which was originally isolated from a gall, *Schisandrae fructus*—and (−)-epigallocatechin gallate (EGCG)—the main constituent of green tea extract (Figure 2)—inhibited the phorbol ester receptor binding with TPA, suggesting that these two polyphenols bind to the receptor of tumor promoter.[5,6] In addition, 5GG and EGCG also inhibited activation of protein kinase C (PKC) by the tumor promoter teleocidin B, a TPA-type tumor promoter.[5,6] In 1987, we first reported that repeated topical applications of 5GG and EGCG inhibited tumor promotion in two-stage carcinogenesis experiments on mouse skin,[5] results that encouraged us to move on to a truly significant project, cancer prevention with green tea.

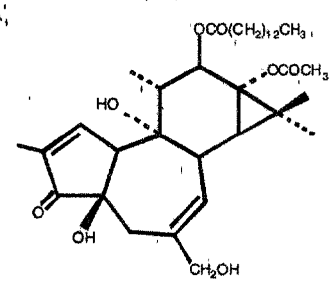
When the Fourth Chemical Congress of North America organized the Symposium on Cancer Chemoprevention in New York in 1991, a US scientist announced at a press conference that green tea extract inhibited lung tumorigenesis in mice, but since animal studies often do not have identical results in humans, he thought more careful studies were needed, before he could recommend green tea for its health effects. But I am from Japan, where Japanese have drunk green tea for 800 years, so I made the following comment: "We Japanese drink green tea every day, and I think that this green tea cannot prevent every cancer, but it is the cheapest and most practical method of cancer prevention available to the general public." The next day, my comment was reported on the front page of *USA Today*. Since then, 13 years have passed and results have built up. Green tea is now an acknowledged cancer pre-

In 1961, Dr. Fujiki became a physician at Kyushu University, Japan. Because he felt that his scientific background at that time was insufficient, he decided to study protein chemistry, especially phylogeny of hemoglobin molecules, at the Max-Planck-Institute for Biochemistry in Munich, Germany. After receiving a great deal of scientific motivation there, he then moved on to study molecular biology at the Biological Laboratories of Harvard University, just in time to be present at the blooming of molecular biology in the lab of Prof. Jim Watson. Returning to the Max-Planck-Institute for Biochemistry, he studied the mechanisms of gene expression for his main subject in Japan, cancer research.

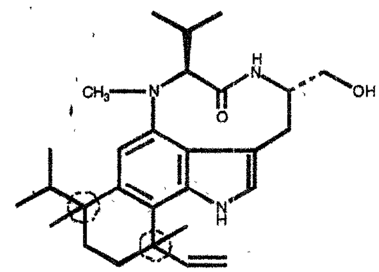
When he was 40 years old, he started cancer research at the National Cancer Center Research Institute in Tokyo, specifically working on tumor promotion and its underlying mechanisms. His research on tumor promotion was greatly advanced by collaboration with distinguished scientists of Japan, the U.S.A., and Germany.

When research in cancer prevention began in Japan in 1983, his group determined to identify original Japanese cancer-preventive agents. In collaboration with Prof. Takuo Okuda, former Professor at Okayama University, the research group demonstrated that (−)-epigallocatechin gallate (EGCG), the main constituent of green tea, bound to the phorbol ester receptor and inhibited both activation of protein kinase C and tumor promotion in two-stage carcinogenesis experiments in mouse skin. This was Dr. Fujiki's first work with green tea, and the first report on EGCG appeared in a new British journal, Phytotherapy Research, in 1987. Further development of his study was conducted at Saitama Cancer Center Research Institute in Japan. At the end of March 2002, he left Saitama Cancer Center upon reaching the compulsory retirement age.

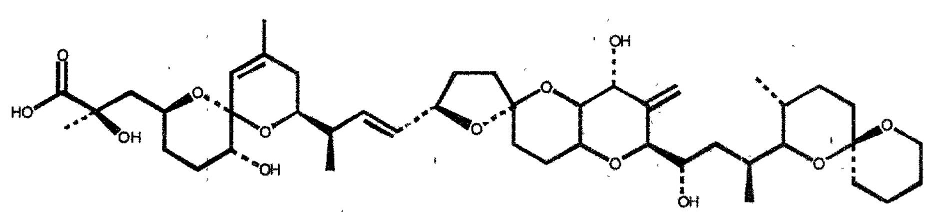
On April 1, 2002, Dr. Fujiki began working as Professor in the Department of Biochemistry, Faculty of Pharmaceutical Sciences, Tokushima Bunri University in Japan, and since February 2003, he has served as Vice-President of this university. He is continuing the study of cancer prevention with green tea for the health of humans. ■



12-*O*-Tetradecanoylphorbol-13-acetate



Teleocidin B



Okadaic acid

Fig. 1. Structures of tumor promoters, TPA, teleocidin B, and okadaic acid. The C-19 and C-22 of teleocidin B shown in a dashed circle have two variable positions, *R* and *S*.

ventive in Japan, and this paper reviews the development of our study of cancer prevention with green tea and the associated international response. I am convinced that my comment is today more valid and widely accepted than ever.

Polyphenols and Phorbol Ester Receptor Binding

Our first test was to examine whether polyphenols shared receptor binding with the tumor promoter phorbol ester, TPA, because this test required minimum amounts of compounds due to the use of radioactive tumor promoter.[4] Most of the polyphenols inhibited the specific ^{3}H-TPA binding dose-dependently at various ED_{50} values (effective dose giving 50% of the maximal response) for inhibition, but some did not.[6] Thirty polyphenols were roughly classified into four classes according to the ED_{50} values (Figure 3). The ED_{50} values of TPA as a control, polyphenols of Classes 1, 2, and 3 were 5.0 nM, 1.7 μM, 30 μM, and 340 μM, respectively.[6] Polyphenols of Class 4 did not bind to the receptor up to 1 mM. Table 1 lists some representatives of the 30 polyphenols according to this classification.[6] Since the ED_{50} values of the Class 1 polyphenols were about 340 times greater than that of TPA, special attention was paid to Class 1 polyphenols, which included penta-*O*-galloyl-β-D-glucose (5GG) and (−)-epigallocatechin gallate (EGCG) (Table 1, Figure 2). Structures of some representative polyphenols of Classes 2, 3, and 4 are shown in Figure 4. How these Class 1 polyphenols with structural diversity could bind to the same phorbol ester receptor with similar ED_{50} values was puzzling: we thought at that time that they might interact with the phorbol ester receptor in the cell membrane differently from TPA.

Okuda and his associates had previously reported that polyphenols have the ability to precipitate water-soluble protein, such as hemoglobin solution. The precipitability of hemoglobin by geraniin, which is a representative tannin isolated from a classic Japanese herb, *Geranium thunberigii* Sieb. *et* Zucc. (*Gennoshoko* in Japanese), was thus taken as a standard control, and the potencies of various polyphenols were compared with results with geraniin: the resulting values were called relative astringency to geraniin (Figure 5).[7] Relative astringency to geraniin was

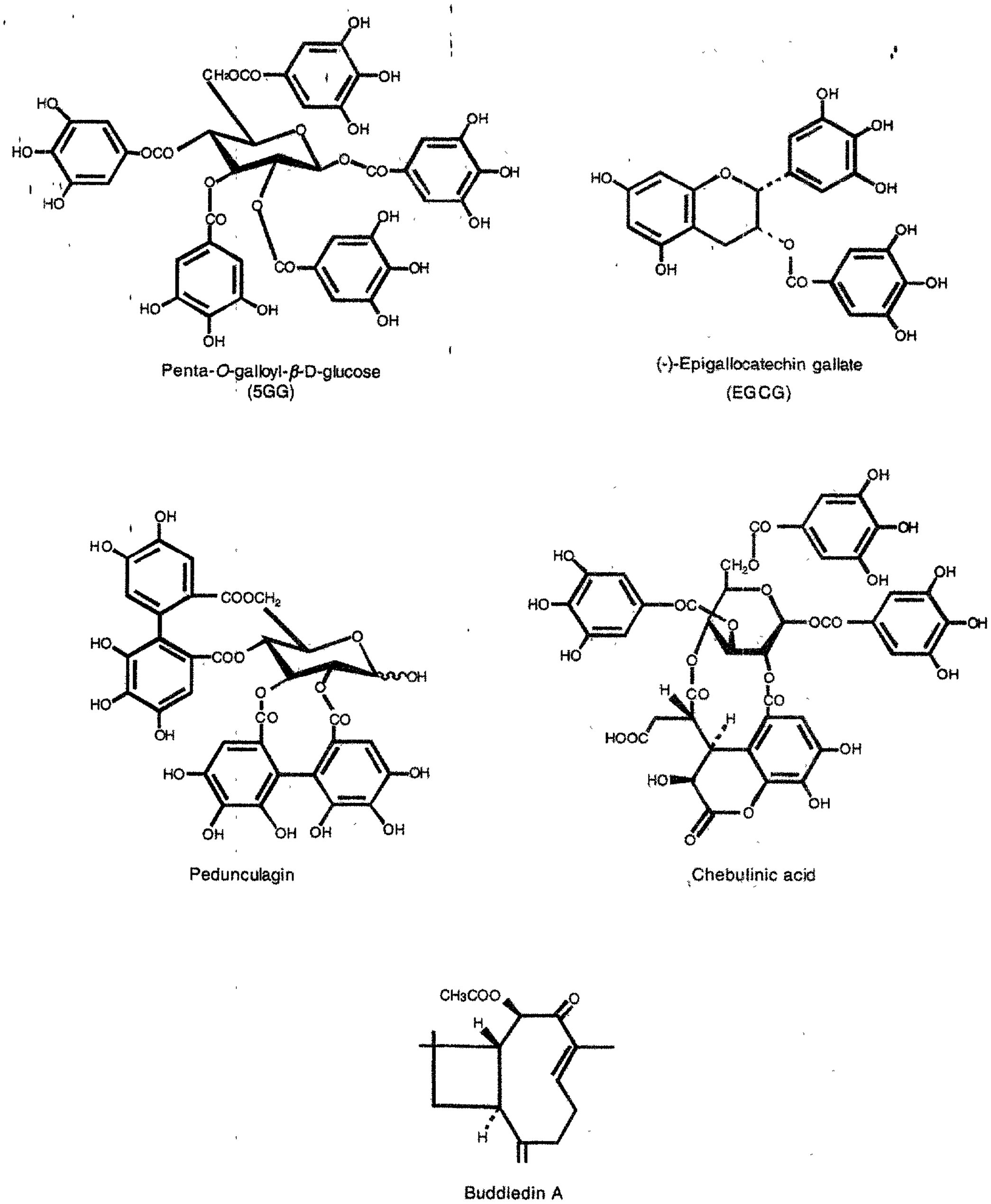


Fig. 2. Structures of Class 1 polyphenols, 5GG, EGCG, pedunculagin, chebulinic acid, and buddledin A.

then used to estimate the biochemical effect of polyphenols resulting from polyphenol–protein interaction. Some polyphenols, such as 5GG and EGCG, showed similar values in two parameters, relative astringency and inhibition of specific binding of ^{3}H-TPA to the receptor (Figure 5).[6]

These results, however, did not clearly show whether 5GG and EGCG were acting as antagonists inhibiting the action of TPA or agonists activating protein kinase C, as does TPA. To differentiate between antagonist and agonist action, 5GG and EGCG were subjected to a test of activation of protein kinase C induced by teleocidin, which is a new activator of protein

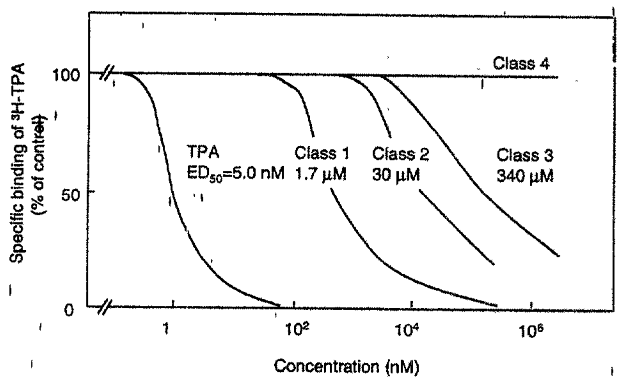
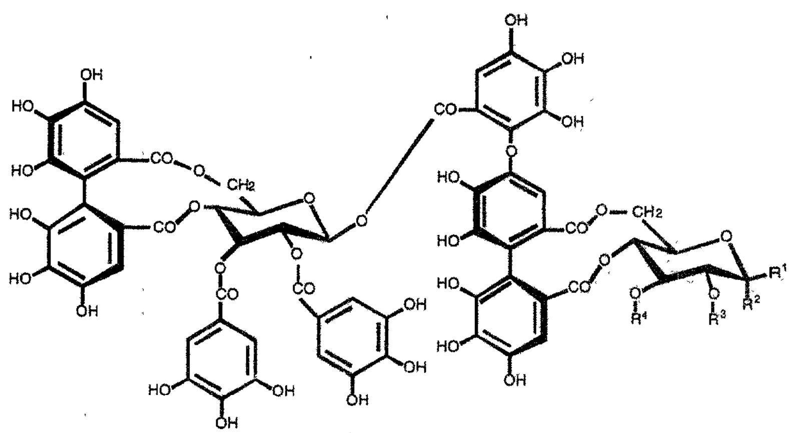


Fig. 3. Classification of polyphenols according to their ED_{50} values for inhibition of specific ^{3}H-TPA binding to a membrane fraction of mouse skin.

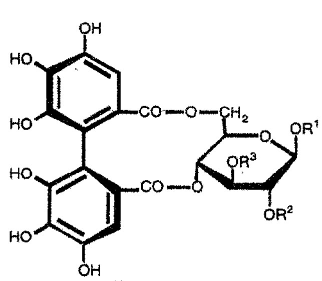
Table 1. Classification of various polyphenols by phorbol ester receptor binding.

Class 1	(ED_{50} = 1.7 µM)
	Penta-*O*-galloyl-β-D-glucose
	(−)-Epigallocatechin gallate
	Pedunculagin
	Chebulinic acid
	Buddledin A
Class 2	(ED_{50} = 30 µM)
	Rugosins D and E
	Coriariin A
	Cornusiin A
	Nobotaniin C
Class 3	(ED_{50} = 340 µM)
	Tellimagrandin I
	Tellimagrandin II
Class 4	(no inhibition)
	(+)-Catechin
	Ellagic acid
	Methyl gallate



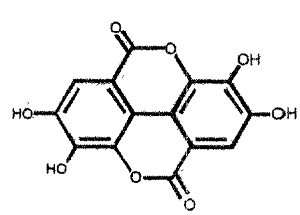
RugosinD

R^1 = O-galloyl, R^2 = H, R^3 = galloyl, R^4 = galloyl



Tellimagrandin I

R^1 = H, R^2 = galloyl, R^3 = galloyl



Ellagic acid

Fig. 4. Structures of some representative polyphenols of Classes 2, 3, and 4.

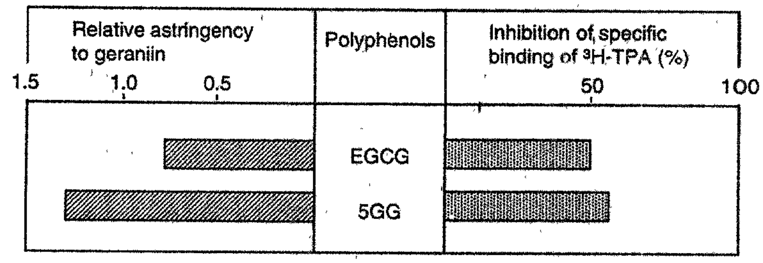


Fig. 5. Biochemical effects of polyphenols on relative astringency to geraniin and inhibition of specific ^{3}H-TPA binding to a membrane fraction of mouse skin. The precipitability of hemoglobin by geraniin was taken as a standard.

kinase C.[8] 5GG and EGCG dose-dependently inhibited the activation of protein kinase C, with ED_{50} values of 1.4 μM and 1.2 μM, respectively.[5,6] These results convinced us that 5GG and EGCG act as antagonists to phorbol ester, and suggested that they inhibit tumor promotion, and are probably not carcinogens.[5,6] This was our first evidence in screening for cancer chemopreventive agents. Thus, 5GG from hydrolysable tannins and EGCG from condensed tannins were selected for further study as cancer chemopreventive agents. Before going on to experiments with costly EGCG, we conducted the first experiment with less expensive 5GG.

5GG and Its Inhibition of Tumor Promotion

A two-stage carcinogenesis experiment consisting of initiation and tumor promotion is an effective system for evaluating the activity of cancer chemopreventive agents. Initiation is usually induced by a single application of a subthreshold dose of a carcinogen, which is called an initiator, but a carcinogen induces only a mutation, not tumor development. Treatment with an initiator followed by repeated applications of a tumor promoter, such as TPA or teleocidin, produces tumors in high percentages on mouse skin, usually 90% to 100% by 10 weeks. An initiator alone or a tumor promoter alone does not produce any tumors.

In studying the processes of the two-stages of carcinogenesis, one notices that initiation is a rapid and irreversible process, while tumor promotion is a long and reversible process. It then follows that inhibition of tumor promotion would seem to be the most practical way to benefit humans. Thus, we utilize the system of inhibition of tumor promotion on mouse skin for the screening of new cancer preventive agents.

To conduct the inhibition of tumor promotion experiment on mouse skin, we had to obtain the compound in sufficient gram amounts. Because molar concentrations of 5GG and TPA for 50% inhibition of phorbol ester receptor binding were 1.7 μM and 5.0 nM, respectively, we thought that 5GG would require 1.7 mg per application to 1 μg TPA, to achieve 50% inhibition of tumor promotion. The required amounts of 5GG were obtained from tannic acid through methanolysis more quickly and cheaply in our laboratory than if we had used EGCG, and this methanolysis cleaved the depside linkage between 5GG and the galloyl group, and resulted in 5GG.[6]

Then 5GG was subjected to a two-stage carcinogenesis experiment on the skin of 8-week-old female CD-1 mice. Specifically, initiation was performed by a single application of 100 μg 7,12-dimethylbenz(a)anthracene (DMBA), and tumor promotion was achieved by repeated applications of 2.5 μg teleocidin B twice a week. In the experimental group, 5 mg 5GG was applied topically 15 min before each treatment with teleocidin B. In this experiment, we used 5 mg 5GG per application because the potency of teleocidin B is comparable to that of TPA. In week 20, the 5GG treatment reduced the percentage of tumor-bearing mice from 100% to 53%, and the average number of tumors per mouse from 3.3 to 0.9,[6] which strongly encouraged us to pursue an experiment with EGCG and to purchase EGCG from a company.

EGCG and Its Inhibition of Tumor Promotion

EGCG is the main polyphenolic constituent of green tea extract. The EGCG used in the experiment was originally isolated from the leaves of Japanese green tea, *Camellia sinensis*, and the inhibition of tumor promotion was performed in a manner similar to that with 5GG. We were again very much encouraged by results like those with 5GG, confirming that the constituent of green tea, EGCG, inhibited tumor promotion on mouse skin, mediated through the inhibition of PKC activation.[5]

We next tested whether EGCG could inhibit tumor promotion of another type of tumor promoter, okadaic acid (Figure 1), which is as potent as TPA and teleocidin on mouse skin, and a potent inhibitor of protein phosphatases 1 and 2A

(PP1 and PP2A).[9] PP1 and PP2A are protein serine/threonine phosphatases 1 and 2A: they release the phosphate group from serine/threonine phosphorylated proteins. Okadaic acid binds to their catalytic subunits and inhibits the activity of PP1 and PP2A (IC_{50}s of 3.4 nM and 0.07 nM, respectively). Inhibition of PP1 and PP2A by okadaic acid induces accumulation of phosphorylated proteins, an effect similar to activation of PKC by TPA or teleocidin.

Specifically, initiation was performed by a single application of 100 μg DMBA on mouse skin, and tumor promotion was achieved by repeated applications of 1.0 μg okadaic acid, twice a week. In the experimental group, 5 mg EGCG was applied topically before each treatment with okadaic acid. As Figure 6 shows, EGCG treatment completely inhibited tumor promotion of okadaic acid up to week 20, with regard to the percentages of tumor-bearing mice and the average number of tumors per mouse.[6] All the results strongly indicated that EGCG inhibited tumor promotion of two tumor promoters associated with two different mechanisms of action.

In 1987, we first reported in a new British journal, *Phytotherapy Research*, that EGCG inhibited tumor promotion on mouse skin, suggesting that EGCG and green tea extract were cancer preventives.[5] Fortunately, the journal *New Scientist* reported our paper in an article entitled "Green tea cuts cancerous growth" in its November 1987 issue.[10] After reading the article, the TV team for the Australian scientific series "Beyond 2000" visited us in Tokyo to make a video about our research. This 8-minute video was shown in Australia, the United States, and other countries, and since then, many scientists have joined the study of green tea as a cancer preventive.

Sealing Effects of EGCG

Since EGCG inhibits two different pathways of tumor promotion, we studied receptor binding using ^{3}H-TPA[4] and ^{3}H-okadaic acid,[11] based on evidence that TPA binds to the phorbol ester receptor, whereas okadaic acid binds to PP1 and PP2A. These two different receptors are present in a membrane fraction of mouse skin. When mouse skin was treated with a single application of 5 mg EGCG, both the specific binding of ^{3}H-TPA and that of ^{3}H-okadaic acid decreased immediately and reached a minimum in 5 to 10 min (Figure 7).[6] The results suggested that when tumor promoters had been applied to mouse skin that was at the lowest level of receptor binding, EGCG treatment possibly inhibited the interaction of tumor promoters with their receptors.[6] Figure 8 is a schematic illustration of the mechanisms of action of EGCG, which we termed the "sealing effects" of EGCG.[6] This was supported by evidence that after human lung cancer cell line PC-9 was treated with ^{3}H-EGCG in culture and subjected to microautoradiography, silver grains of ^{3}H-EGCG appeared in the membrane, cytosol, and nuclei.[12]

Dr. Shunsaku Kimura and his associates at the Department of Chemistry, Kyoto University, studied the effects of EGCG from the physicochemical viewpoint.[13] EGCG inhibited PKC activation in the presence of dimyristoylphosphatidylcholine liposome, which indicated that the inhibitory effects of EGCG are influenced by the lipid type. Kimura's group also found that the ATP-binding site of PKC is located at the membrane surface, which is very close to EGCG in the membrane, leading to a strong inhibition of ATP binding by

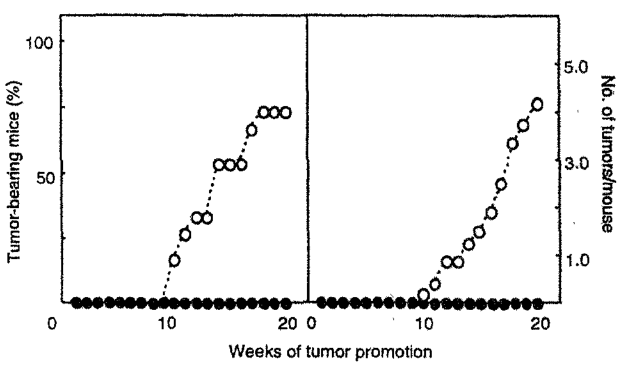


Fig. 6. Inhibition of tumor promotion on mouse skin by EGCG. Groups were treated with DMBA and okadaic acid (○) and with DMBA and okadaic acid plus EGCG (●).

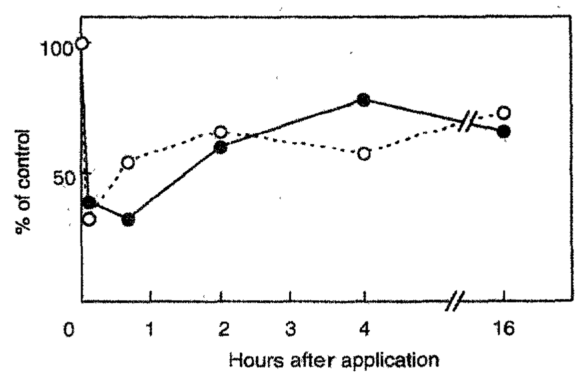


Fig. 7. Inhibition of specific binding of ^{3}H-TPA and ^{3}H-okadaic acid to a membrane fraction of mouse skin after a single application of EGCG. ^{3}H-TPA (●) and ^{3}H-okadaic acid (○).

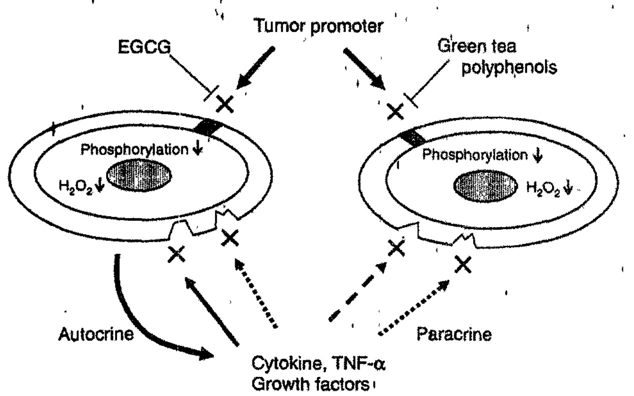


Fig. 8. A schematic illustration of the mechanisms of action of EGCG, the "sealing effects" of EGCG.

EGCG. Since TPA acts as a boundary lipid, it is now thought that TPA and EGCG bind competitively to PKC in the lipid bilayer membrane. The group also studied the effects of EGCG on PP2A activity. EGCG recovered inhibition of PP2A activity by okadaic acid, suggesting that EGCG forms aggregates in a buffer solution. All the results confirmed the sealing effects of EGCG on proteins, both directly and indirectly.[13]

Green Tea Extract

Green tea is a non-oxidized, non-fermented product containing at least four tea polyphenols, (–)-epigallocatechin (EGC), EGCG, (–)-epicatechin (EC), and (–)-epicatechin gallate (ECG) on HPLC (Figure 9A). The usual composition is 10–15% EGCG, 6–10% EGC, 2–3% ECG, and 2% EC. EGCG is the main constituent of green tea extract, and the highest peak on HPLC is caffeine. In Japan, there are numerous types of green tea, including sencha and hojicha. Sencha is the most popular kind of green tea in Japan, and hojicha is tea made from roasted bancha leaf which is the lowest grade of sencha. Table 2 shows the composition of green tea polyphenols in sencha compared with that in hojicha: sencha contains 5 times more tea polyphenols than inexpensive hojicha, but contains the same amount of caffeine. Oolong tea is the partially oxidized fermented product (Table 2), and black tea is the fermented product containing more theaflavins and thearubigins (Figure 9B) than catechins, and fewer polyphenols. These teas are also derived from the same plant, *Camellia sinensis.* Various green tea polyphenols dose-dependently inhibited the growth of the human lung cancer cell line PC-9, with the order of potency being ECG, EGCG, and EGC. Epicatechin, EC, was not effective here. The number of viable cells was counted by use of the trypan blue dye exclusion test and the number of non-treated cells was taken as 100% (Figure 10).[12]

Dr. Masami Suganuma, my colleague at Saitama Cancer Center discovered the synergistic enhancement of EC, an inactive tea polyphenol, with EGCG, in an experiment with ^{3}H-EGCG incorporation into PC-9 cells (Figure 11).[14] EC enhanced ^{3}H-EGCG incorporation into the cells by 1.5 times, suggesting that the presence of EC facilitates ^{3}H-EGCG incorporation into cells. In addition, Dr. Suganuma found that EC also enhanced incorporation of ECG and EGC into cells in a manner similar to EGCG. The synergistic effects of EC with green tea polyphenols were also proved by three criteria: induction of apoptosis in PC-9 cells, growth inhibition of PC-9 cells, and inhibition of tumor necrosis factor-α (TNF-α) release from BALB/3T3 cells induced by okadaic acid.[14] BALB/3T3 cell is a cultured cell line of fibroblasts obtained from fetal mouse of BALB/C strain. These results strongly indicated that a mixture of green tea extract, i.e., whole green tea, is a more effective and practical cancer preventive than EGCG alone.

Cancer Preventive Activity

Cancer preventive activity can be understood by inhibition of tumor promotion in a two-stage carcinogenesis experiment, as reported previously. However, because animal experiments are tedious and time-consuming, we usually look at biological and molecular markers, such as *TNF-α* gene expression and TNF-α release from cells, which are induced by a tumor promoter in cells and are essential for tumor promotion *in vivo.* We can thus determine the activity of the markers in an *in vitro* cell culture system, and quantitatively evaluate the inhibitory potency of a molecular marker: this is the cancer preventive activity.

Although the study of tumor promotion in rodent carcinogenesis using TPA and okadaic acid has revealed two different pathways of tumor promotion, application of TPA and okadaic acid both induced *TNF-α* gene expression in mouse skin.[15] This is why cancer is sometimes called a TNF-α disease or a NF-κB disease: the proinflammatory cytokine TNF-α is an endogenous tumor promoter that induces NF-κB activation, leading to cell proliferation.[16–19] In the light of this evidence, we obtained results showing that numerous inhibitors of tumor promotion inhibited both *TNF-α* gene expression and TNF-α release, resulting in a reduction of the amount of this endogenous tumor promoter in cancer cells and surrounding tissues, leading to growth inhibition of cancer.[15] Lifestyle related diseases, such as rheumatoid arthritis and other autoimmune diseases are also thought to be TNF-α or NF-κB diseases, so in this section I will discuss the cancer preventive activity of green tea in relation to TNF-α reduction.

We decided to quantitatively measure inhibition of TNF-α release from cells treated with okadaic acid, rather than inhibition of *TNF-α* gene expression and NF-κB activation

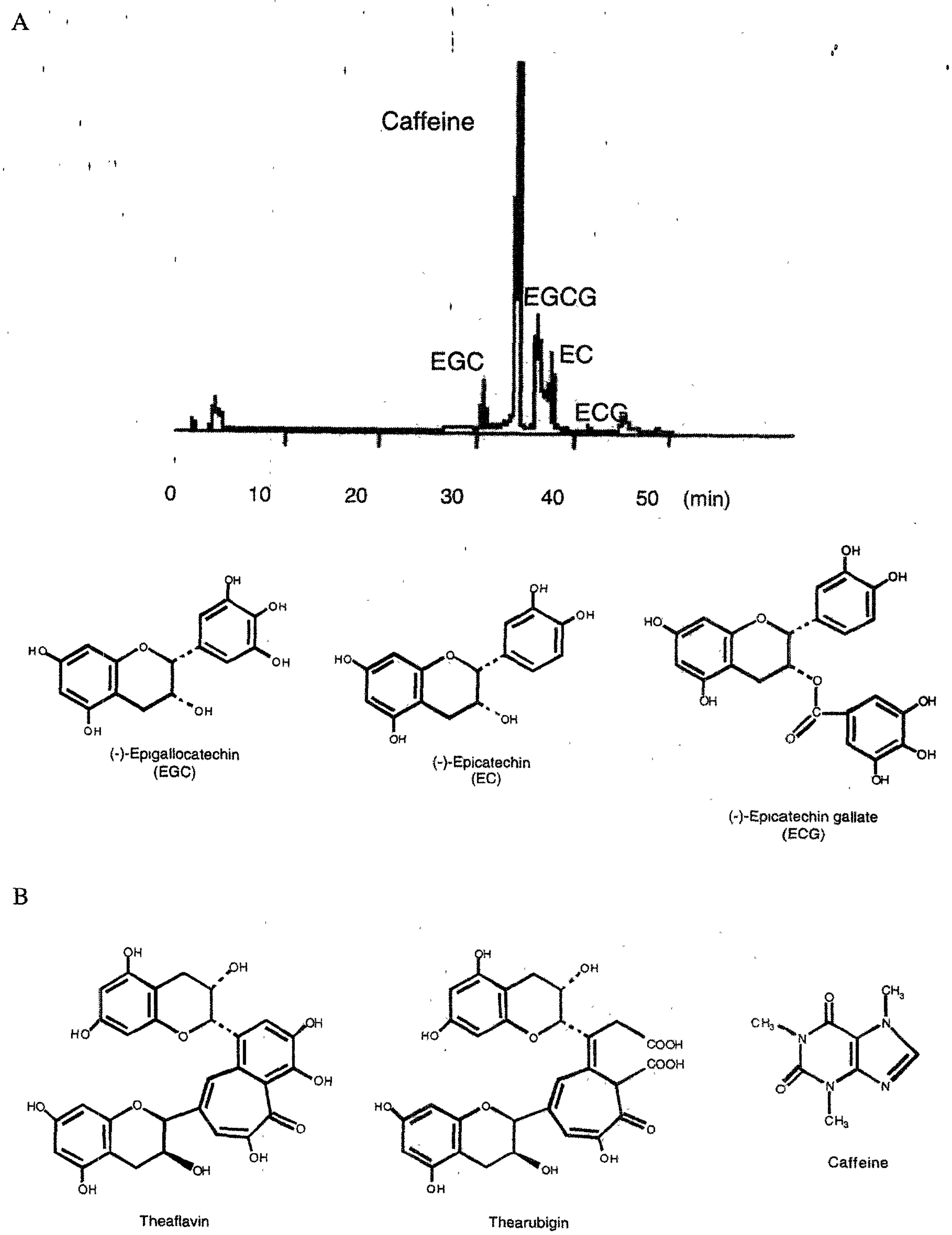


Fig. 9. A. HPLC of green tea extract and structures of EGC, EC, and ECG. B. Structures of theaflavin, thearubigin, and caffeine.

Table 2. The composition of green tea polyphenols in various teas. (%)

	EGCG	EGC	ECG	EC	Total	Caffeine
Sencha	7.51	3.81	1.43	0.86	13.61	2.62
Hojicha	1.68	0.56	0.56	0.16	2.96	2.06
Oolong tea	4.67	1.74	0.88	0.33	7.62	2.28

Tea Experiment Station of Saitama Prefecture

Sencha: The most popular kind of green tea in Japan.
Hojicha: Tea made from roasted bancha leaf, which is the lowest grade of Sencha.
Oolong tea: Leaves are partially oxidized.

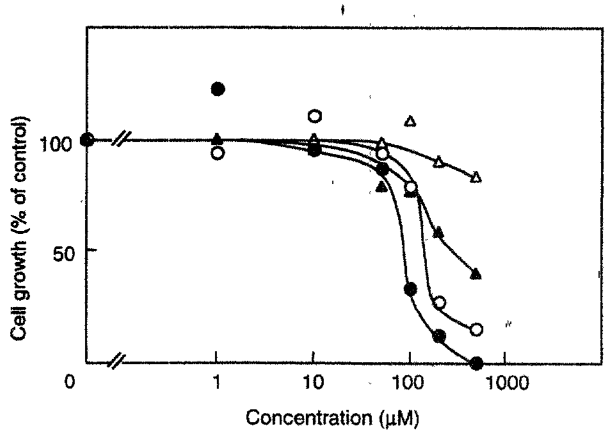


Fig. 10. Growth inhibition of human lung cancer cell line PC-9 by green tea polyphenols. PC-9 cells (2×10^5/ml) were treated with various concentrations of ECG (●), EGCG (○), EGC (▲), or EC (△) for 3 days. The number of viable cells was expressed by means of the dye exclusion method. SD was deleted from the original figure.[12]

directly.[20] ECG, EGCG, and EGC dose-dependently inhibited TNF-α release from human stomach cancer cell line, KATO III, treated with okadaic acid, whereas EC did not.[21] Although EC is an inactive polyphenol, cotreatment with EC and EGCG, and EC and other tea polyphenols, synergistically enhanced inhibition of TNF-α release, as mentioned previously.[14] It is interesting to note that inhibition of TNF-α release from KATO III cells by green tea polyphenols is very similar to that of growth inhibition of PC-9 cells by them, as shown in Figure 9.[12] We believe that inhibition of *TNF-α* gene expression correlates well with inhibition of cancer cell growth.[22]

The important features of EGCG and green tea extract as cancer preventives should be briefly summarized.[23–28] 1. EGCG and green tea extract are non-toxic for rodents and humans. 2. They have a wide range of target organs, such as the digestive tract including esophagus, stomach, duodenum, and colon, plus liver, lung, pancreas, and skin. Recently, breast,

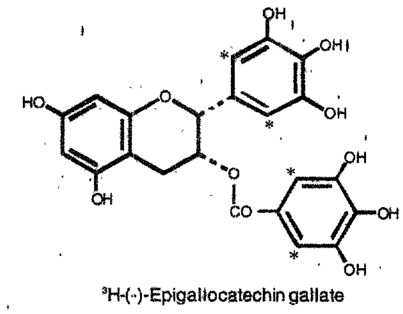


Fig. 11. Structure of ^{3}H-EGCG. *Potential ^{3}H labeled positions were estimated by ^{3}H NMR.

bladder, and prostate have been added to the list.[23–28] This wide range of target organs makes green tea significantly different from standard cancer preventive drugs. 3. They have inhibitory effects on growth of cancer cells associated with G_2/M arrest in human lung cancer cell line, PC-9.[12] 4. EGCG in drinking water showed inhibitory effects on lung metastasis of B16 melanoma cells.[27]

In 1994, the *New York Times* reported the cancer preventive effects of green tea in a story entitled "Green tea, more than just a soothing brew." This article was supported by a report from Shanghai that green tea may reduce the incidence of cancer of the esophagus in humans. I got the impression that the significance of drinking green tea for cancer prevention in humans was beginning to be widely recognized in Western countries.

Distribution of ^{3}H-EGCG in Organs

From the above-mentioned systemic effects of EGCG and green tea, we assumed that EGCG and green tea polyphenols are easily distributed from the digestive tract to various organs, where they induce anticarcinogenic effects. To prove this, we obtained ^{3}H-EGCG with a specific activity of 48.1 GBq/mmol. 4(n)-[^{3}H](–)-EGCG was labeled with tritium gas by Amersham, Aylesbury, UK,[29] and the positions labeled with ^{3}H were found in one of the aromatic rings estimated from the ^{3}H-NMR (Figure 11). It was fortunately a very stable compound, which was also used for the study of ^{3}H-EGCG incorporation into PC-9 cells and that of microautoradiography of ^{3}H-EGCG in the cells, as previously reported.[12]

^{3}H-EGCG was administered into the mouse stomach, and within 24 h of administration, 6.6% of total administered radioactivity was excreted in urine and 37.7% in feces. Twenty-four hours after intubation, various amounts of the total administered radioactivity were found in the digestive tract, liver, brain, kidney, lung, pancreas, and skin. The results strongly indicated that the radioactivity was present in the organs where EGCG and green tea extract had previously been shown to inhibit carcinogenesis.[29]

Since we Japanese drink green tea throughout the day, we wondered if duplicated administrations of ^{3}H-EGCG would enhance radioactivity in the organs. For a single administration, ^{3}H-EGCG was administered into the mouse stomach and radioactivity in various organs was determined 6h later. For duplicate administrations, the first and second administrations of ^{3}H-EGCG were given 6h apart, and the radioactivity in the organs was similarly determined 6h after the second administration. When the radioactivity in the various organs after a single administration and after duplicate administrations was compared, duplicate administrations enhanced incorporation of ^{3}H-EGCG by 4 to 9 times in most organs.[29] Radioactivity in blood and urine increased as well. We named this synergistic enhancement by EGCG the "Fujiki–Suganuma Effect," which allows us to think that the more green tea we drink, the higher the concentration of EGCG we get in the target organs.

To extend our study on the enhanced effects of duplicate administrations at the molecular level, human lung cancer cell line A549 was treated with EGCG from one to four times at 6h intervals. We found that the expression of growth arrest and DNA damage-inducible gene (*GADD153*) was continuously enhanced depending on increased administrations, and that of the cyclin-dependent kinase inhibitor gene (*p21*^{WAF1}) was also enhanced.[30] Thus, multiple administrations of EGCG can easily increase the concentration of green tea polyphenols in the cells, and probably reach effective concentrations in vivo. This synergistic effect by multiple administrations of EGCG made it possible to link the high concentrations of EGCG in the cell culture experiment and daily consumption amounts of green tea beverage in humans.

Epidemiological Study on Health Benefits for Humans

The question of whether green tea has measurable cancer preventive effects for humans was answered in the results of a prospective cohort study conducted by Drs. Kei Nakachi and Kazue Imai.[31] We were fortunate to have previously worked together at Saitama Cancer Center, which is located in Saitama Prefecture, a green tea producing area in Japan.

In 1986, Nakachi and Imai surveyed 8,552 individuals aged over 40 with 90 questions on their living habits, including daily consumption of green tea. During the 10 years after 1986, our colleagues found a total of 419 cancer patients, 244 males and 175 females, among the participants in the cohort study. Table 3 shows the average age at cancer onset and daily green tea consumption (cups/day) of cancer patients. Cancer onset of patients who had consumed over 10 cups of green tea per day was 7.3 years later among females, and 3.2 years later among males, than those of patients who had consumed less than three cups per day.[31] The difference between females and males is partly due to higher tobacco consumption by males. Since the most effective indication of cancer prevention in humans is delayed cancer onset, this was the first clear evidence that drinking lots of green tea gives us longer, healthier lives. The results allowed us to determine the effective cancer preventive amount to be 10 Japanese-size cups (about 120 ml/cup) of green tea per day, about 2.5 g green tea extract. We now recommend taking this amount daily for the general population: This first stage of cancer prevention with green tea leads to delay of cancer onset (Figure 12).[32]

Table 3. Delayed cancer onset with daily green tea consumption (over 10 cups) from cancer patients in Saitama Prefecture.

	Green tea consumption (cups/day)		
	≤3	4–9	≥10
Females			
Average age at cancer onset	67.0 ± 1.7	66.4 ± 1.3	74.3 ± 2.2
(No. of cancer patients 175)	(49)	(102)	(24)
Males			
Average age at cancer onset	65.0 ± 1.5	67.2 ± 1.0	68.2 ± 1.1
(No. of cancer patients 244)	(59)	(114)	(71)

Nakachi and his associates found decreased recurrence of human breast cancer with increased consumption of green tea, from results obtained from 472 cancer patients at Saitama Cancer Center Hospital. In stage I and II cancer patients, the group consuming over five cups per day showed a lower recurrence rate, 16.7%, and a longer disease-free period, 3.6 years, than those consuming fewer than four cups per day, 24.3% and 2.8 years, respectively.[33] However, advanced breast cancer of stage III was not preventable. This suggests that green tea is more effective in the early stage of second tumor development, even after removal of the primary cancer, which will probably lead to more hopeful prognoses for breast cancer patients.[33]

Encouraged by the results, we moved on to cancer prevention for patients after cancer treatment, knowing that Japanese clinicians are eager to prevent recurrence of cancers.[34] We obtained some exciting results on prevention of polyp development after colorectal polypectomy, by those consuming 10 cups of green tea supplemented with green tea tablets produced by the Tea Experiment Station of Saitama Prefecture (Moriwaki, personal communication). We call this the second stage of cancer prevention with green tea for patients following cancer treatment (Figure 12).[32]

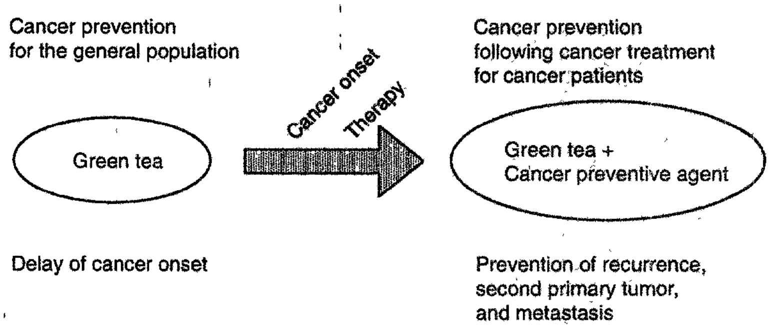


Fig. 12. Two stages of cancer prevention with green tea: before cancer onset for the general population and following cancer treatment for patients.

The late Ernst Wynder, a famous scientist in the field of epidemiology at the American Health Foundation, Valhalla, New York, had studied lung cancer and cigarette smoking, and first introduced a filter into cigarettes many years ago. His colleagues raised the question of why Japanese smokers had a lower incidence of lung cancer than American smokers even though Japanese and American smokers consumed similar amounts of tobacco: the average numbers of cigarettes per day in 1985 were 24.6 for Japanese and 22.8 for Americans, whereas age-adjusted death rates per 100,000 from 1986 to 1988 were 28.6 for Japanese and 56.9 for Americans.[35] Wynder and Hoffmann reported in 1994 that the astonishing difference in lung cancer incidence rates was probably due to different consumed amounts of tea: estimated annual per capita consumption of tea from 1987 to 1989 was 0.96 kg green tea for Japanese and 0.34 kg black tea for Americans.[35] In addition, their colleagues reported that green tea extract inhibited lung tumorigenesis more strongly than did black tea extract.[25] We thank Dr. Wynder for his enormously encouraging findings.

Combination Cancer Prevention

The term "Combination cancer prevention," coined by M. Sporn was based on evidence that the combined use of several drugs with different mechanisms of action exerted marked synergistic preventive effects.[36] We realized that many Japanese cancer patients take cancer preventive drugs and also drink green tea without knowing its cancer preventive activity. Japanese cancer patients are thus performing combination cancer prevention. Here, I will discuss the significant enhancement of cancer preventive activity by cotreatment with EGCG or green tea and a cancer preventive drug.

My colleague, M. Suganuma, demonstrated that treatment with EGCG and sulindac, a cancer preventive drug, induced apoptosis of PC-9 cells 20 times greater than did EGCG or sulindac alone.[14] Sulindac sulfide, an active form, also showed enhanced apoptosis with EGCG, in much lower concentrations than sulindac. Moreover, the number of tumors per mouse among multiple intestinal neoplasia (Min) mice was reduced from 72.3 to 32 by a combination of green tea and sulindac, a decrease of 55.7%.[37]

To understand the molecular mechanisms of synergistic effects on EGCG and sulindac, the expression patterns of the genes in the PC-9 cells treated with EGCG plus sulindac, EGCG alone, sulindac alone, and non-treated cells as control were compared.[38] Table 4 shows that cotreatment with EGCG and sulindac induced dramatic new up-regulation of *GADD153* and *p21*^{WAF1} gene expressions, about 12-fold and 3-fold enhancement, respectively.[39] These genes were discussed previously. Another four genes were down-regulated to less than 0.3-fold by cotreatment.[39] In addition, our research group extended the study on combination cancer prevention, using

Table 4. Effects of cotreatment with EGCG and sulindac on gene expression.

	Relative expression level compared with control (fold)		
Genes	EGCG	Sulindac	EGCG + Sulindac
Up-regulated			
GADD153	0.87	0.78	11.61
p21^{WAF1}	1.02	1.43	2.97
Down-regulated			
T-plasminogen activator	1.87	0.64	0.05
TIMP3	0.77	0.74	0.29
IL-1β	0.78	0.95	0.30
Integrin β4	0.87	0.89	0.34

EGCG with retinoids. Cotreatment with EGCG plus all-*trans*-retinoic acid and EGCG plus 9-*cis*-retinoic acid also showed synergistic induction of *GADD153* gene expression and apoptosis, whereas that with EGCG plus 4-hydroxylphenylretinamide showed only additive effects.[40] It seems likely that combination cancer chemoprevention with green tea works for Japanese cancer patients by inducing a new additional cancer preventive pathway, and by reducing the dosage and side effects of cancer preventive drugs.

Prof. Jim Watson's Comments

In May 2002, I was fortunate to be able to participate in the International Conference on Green Tea and Cancer: A Critical Review, held at the Banbury Center of Cold Spring Harbor Laboratory. This conference was strongly supported by the Director, Prof. Jim Watson. However, remembering my time as a postdoc in his lab at Harvard University in 1970, I wondered whether Dr. Watson had real interest in cancer prevention with green tea, since he was/is a pioneer of molecular biology. Dr. Watson listened closely while one of the organizers noted the success of the conference. When the organizer told him that the human epidemiological studies had proved inconclusive, Dr. Watson immediately answered that since green tea prevented carcinogenesis in rodents, it should prevent it in humans as well, since humans and mice have similar genomes. It was strong encouragement for green tea scientists like me, and I got the impression that Dr. Watson now believes in the cancer preventive effects of green tea in humans. I was very pleased with the outcome of this conference, and gratified to find increasing interest in green tea.

On the way back to Japan, I started to write the manuscript of my presentation at the Banbury Center. The manuscript appeared in the December 2002 issue of *Cancer Letters*.[32] In February 2003, I received an e-mail from the publisher informing me that our paper entitled, "Green tea: cancer preventive beverage and/or drug," was one of the 20 most downloaded articles from the journal in 2003. This e-mail was confirmation that interest in green tea is spreading all over the world.

Conclusion

Japanese people have the longest life span in the world: 85 years for females and 78 years for males. When the Japanese priest Eisai, who brought seeds of the green tea plant to Japan as a medicine in 1191, wrote a book entitled "Kitsusa youjouki" ("Maintaining Health by Drinking Green Tea") in 1211, Eisai was 81 years old. We have now learned that many life-style related diseases including cancer can be partially prevented by green tea and healthy lifestyles.[41,42] It is indeed gratifying to me to see Eisai's visionary discovery put into practice some 800 years after he brought green tea to Japan with such great expectations. This cancer prevention study on EGCG and green tea is based on the tradition of Japanese culture, polished by the knowledge of natural product chemistry, which I learned from Prof. Adolf A. Butenandt at the Max-Planck Institute for Biochemistry in Munich, and the concept of cancer chemoprevention derived from US cancer researchers.

This work was supported by Scientific Research on Priority Areas for Cancer Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan; Encouragement of Young Scientists from the Japan Society for the Promotion of Science of Japan; Comprehensive Research on Aging and Health; and Cancer Research from the Ministry of Health, Labor, and Welfare; Japan. Selectively Applied and Developed Research, and Green Tea Extracts Research Development for Cancer Prevention by the Department of Agriculture and Forests and the Department of Health and Human Services of Saitama Prefecture, Japan; and the Smoking Research Fund. I thank Dr. Takashi Sugimura, President Emeritus of the National Cancer Center, for his encouragement during the course of this work, and Profs. Takuo Okuda and Takashi Yoshida at the Faculty of Pharmaceutical Sciences of Okayama University. I also thank Prof. Shunsaku Kimura at the Department of Chemistry, Kyoto University, for his stimulating collaborations, and Mr. Yoshiaki Kitaoka, Mr. Kenta Nakajima, and Mr. Itaru Okada at the Department of Agriculture of Saitama Prefecture for their fruitful discussions. For her excellent contribution to this work, I heartily thank my close and longstanding coworker, Dr. Masami Suganuma, who worked with me at the National Cancer Center Research Institute in Tokyo and Saitama Cancer Center, and express my gratitude to other scientists for their meaningful collaboration. These include Drs. Sachiko Okabe-Kidokoro, Kei Nakachi, Kazue Imai, Atsumasa Komori, Eisaburo Sueoka, Naoko Sueoka, Yuri Goto, Satoru Matsuyama, and Nobukazu Fujimoto, and Mrs. Ikuko Shiotani and Ms. Kaori Suzuki along with Ms. Miki Kurusu who worked with me at the Saitama Cancer Center Research Institute.

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Dockets

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Year 2004

Docket No.	Title of Docket
2004N-0559	Overall Benefit to Risk Considerations for COX-2 Selective Nonsteroidal Anti-Inflammatory Drugs and Related Agents (New 5/5/05)
2004N-0545	Nonclinical and Clinical Datasets; Notice of Pilot Project (New 3/22/05)
2004D-0524	Draft Guidance for Industry on and as: Pharmaceutical Solid Polymorphism; Chemistry, Manufacturing, and Controls Information
2004V-0536	Laser Light Show (New 12/16/04)
2004N-0535	Agency Information Collection Activities; Proposed Collection; Medwatch: the FDA Medical Projects Reporting Program; Comment Request (New 3/22/05)
2004N-0534	Agency Information Collection Activities; Proposed Collection; Comment Request; Format and Content Requirements for Over-the-Counter (OTC) Drug Product Labeling (New 3/8/05)
2004P-0523	Generic Fluticasone Propionate Nasal Spray Products Meet the Same High Standards of Quality as GSK's Brand-name Product Lonase
2004D-0510	Live & Perishable Fish & Fishery Products for Export to the European Union and the European Free Trade Association (New 2/28/05)
2004D-0484	2004D-0484: Guidance for Industry on the Role of HIV Drug Resistance Testing in Anteiretroviral Drug Development (New 3/11/05)
2004D-0465	Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDS) (New 3/3/05)
2004D-0460	Guidance for Industry on Listed Drugs, 30-Month Stays, and Approval of ANDAs and 505(B)(2) Applications Under Hatch-Waxman, as Amended by the Medicare Prescription Drug, Improvement, and Modernization (New 2/28/05)
2004D-0459	Guidance for Industry on Pharmacokinetics in Pregnancy Study Design, Data Analysis and Impact on Dosing and Labeling (New

	3/22/05)
2004N-0454	Dietary Supplements; Premarket Notification for New Dietary Ingredient Notifications; Public Meeting (New 12/9/04)
2004D-0443	Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Regulations (Updated 3/3/05)
2004D-0440	Guidance for Industry on Computerized Systems used in Clinical Trials (Updated 3/3/05)
2004N-0423	Second Annual Stakeholder Meeting on the Implementation of the Medical Device User Fee and Modernization Act of 2002 Provisions, Public (New 1/13/05)
2004N-0408	Regulatory Site Visit Training Program (New 12/9/04)
2004P-0386	Reject New Drug Application 21-695
2004D-0378	International Conference on Harmonisation; Draft Guidance on S7B Nonclincial Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals
2004D-0377	International Conference on Harmonisation; Draft Guidance on E14 Clinical Evaluation of QT/QTC Interval Prolongation and Proarrhythmic Potential for N0n-Antiarrhythemic Drugs
2004D-0369	Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by Bioengineered Plants Intended for Food Use (New 3/22/05)
2004D-0343	Hospital Bed System Dimensional Guidance to Reduce Entrapment (Updated 2/25/05)
2004F-0374	Amend Food Additive Regulations in 172.380 Vitamin D3 to Permit the Use of Vitamin D3 in Cheese and Cheese Products at a Level Above That Permitted Under 184.1950 Vitamin D (New 10/05/04)
2004N-0355	Scientific Considerations Related to Developing Follow-on Protein Products (New 11/12/04)
2004N-0337	Subpart D IRB Referral, Effects of a Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder; a Functional Magnetic Resonance Study (Updated 9/15/04)
2004D-0330	Suicidality in Clinical Trials for Antidepressant Drugs in Pediatric Patients (Updated 9/15/04)
2004H-0322	Civil Money Penalty Re: Ecumed Health Group, Inc. (New 3/3/05)
2004P-0320	Refrain from Approving Certain Applications Submitted Under Section 505(B)(2) of the FDCA that Rerference Depakote (Divalproex Sodium Delayed-Release Tablets) (New 12/1/04)
2004P-0299	Nutrient Content Claims for Carbohydrates (New 2/25/05)
2004P-0298	Nutrient Content Claims for the Carbohydrate Content of Food (Updated 2/25/05)
2004P-0297	Nutrient Content Claim: DefineTerms Low Carbohydrate, Reduced Carbohydrate, Reduced Carbohydrate and Carbohydrate Free

	(New 10/19/04)
2004D-0283	Waivers of In Vivo Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles (New 10/05/04)
2004V-0277	Laser Light Show (New 1/25/05)
2004P-0276	Initiate Proceedings to Permit Computerized Thermal Iimaging, Inc. (CTI) to Supplement the Administrative Record in Connection with CTIS Premarket Approval Application in P010035 (New 1/25/05)
2004P-0271	Determine that Drying Lotion, a Topical Acne Drug Products for Over the Counter Human Use, can Contain in Combination Both Sulfur (10.0%) and Salicylic Acid (2.0%) as the Active Ingredients (New 1/25/05)
2004S-0270	Notice Announcing Publication of the Report to Congress Entitled "Plan for the Transfer of Responsibility for Medicare Appeals" and Soliciting Comments (New 8/09/04)
2004N-0257	Recordkeeping Requirements for Human Food and Cosmetics Manufactured from Processed with, or Otherwise Containing Material from Cattle (New 10/04/04)
2004S-0233	Stimulating Innovation in Medical Technologies(Updated 12/22/04)
2004N-0221	Medicare Prescription Drug, Improvement, and Modernization Act of 2003 Section 107(F) B (Updated 9/15/04)
2004N-0217	Nutrient Content Claims: DHA, PEA, and ALA (Omega-3-Fatty Acids) (New 12/9/04)
2004N-0214	Public Information Regulations (New 10/25/04)
2004S-0212	Pandemic Influenza Preparedness and Response Plan (New 11/10/04)
2004D-0210	Guidance: Clinical Trial Design for Hip Replacement Systems (New 5/10/04)
2004Q-0201	Qualified Health Claim (QHC); Lycopene, Tomatoes and Cancer (Updated 3/8/05)
2004P-0183	Nutrient Content Claim: Expand the Definition of Lean (New 4/27/04)
2004N-0181	Critical Path Initiative (Updated 11/16/04)
2004Q-0180	Qualified Health Claim (QHC): Lutein and Eye Diseases (Updated 2/1/05)
2004P-0171	Standards for 'Similarity' or 'Sameness' of Biotechnology-derived Products (New 5/4/05)
2004S-0170	Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Section 1013: Suggest Priority Topics for Research (Updated 7/13/04)
2004P-0164	Exemption from the Medical Devices Tracking Requirements for Heartstream automated External Defibrillators (New 12/02/04)
2004V-0155	Valley Forge Composite Technologies Explosive Detection

	Systems (New 12/16/04)
2004Q-0151	Qualified Health Claim (QHC): Soy Protein and Cancer (Updated 4/29/05)
2004Q-0144	Qualified Health Claim (QHC): Chromium Picolinate and Diabetes (Updated 12/1/04)
2004N-0133	Part II, Electronic Record; Electronic Signatures; Public Meeting (Updated 9/13/04)
2004N-0115	Prescription Drug Importation; Public Meeting (Updated 7/13/04)
2004P-0110	Nutrient Content Claim: Carbohydrate Content in Food (Grocery Manufactures of America) (New 3/12/04)
2004P-0107	Nutrient Content Claim: Carbohydrate Content in Food (ConAgra Foods) (New 3/1/04)
2004P-0105	Nutrient Content Claim: Carbohydrate Content in Food (Kraft Foods North America Inc) (Updated 5/4/05)
2004Q-0102	Qualified Health Claim (QHC): Calcium and Kidney/Urinary Stones (Updated 10/19/04)
2004Q-0100	Qualified Health Claim (QHC): Calcium and Bone Fractures (Updated 1/31/05)
2004Q-0099	Qualified Health Claim (QHC): Calcium and Menstrual Disorders (Updated 10/25/04)
2004Q-0098	Qualified Health Claim (QHC): Calcium and Hypertension (New 10/25/04)
2004Q-0097	Qualified Health Claim (QHC): Calcium and Various Cancers (Updated 10/21/04)
2004Q-0083	Qualified Health Claim (QHC): Green Tea and Reduced Risk of Cancer (Updated 3/3/05)
2004N-0081	BSE Risk Materials in Foods and Cosmetics (New 11/8/04)
2004Q-0072	Qualified Health Claim (QHC) for Eggs with Enhanced Omega-3 Fatty Acid Content and a Balanced 1:1 Ratio of Omega-3/Omega-6 Fatty Acids and Reduced Risk of Heart Disease and Sudden Fatal Heart Attack (Updated 5/4/04)
2004P-0060	Health Claim Petition: Glucosamine Sulfate and Osteoarthritis (Updated 2/25/05)
2004P-0059	Health Claim Petition: Glucosamine and Chondroitin Sulfate and Osteoarthritis (Updated 11/24/04)
2004N-0033	Factor VIII Inhibitors, Public Workshop (New 7/15/04)
2004N-0018	Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application (New 1/7/05)
2004P-0015	Deny Approval of any New Drug Application (NDA) for Recombinant Salmon Calcitonin (RESCT) Nasal Spray (New 5/5/05)

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